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# **Pain patterns during adolescence can be grouped into four pain classes with distinct profiles: A study on a population based cohort of 2953 adolescents**

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## ABSTRACT

**Introduction:** Although multi-site pain is common in adolescents, pain conditions are frequently diagnosed and treated in isolation. Little is known about whether there are specific sites in which pain commonly co-occurs. This study examines patterns of pain in adolescents, and whether these are associated with sports participation, health related quality of life (HRQoL), and sex.

**Methods:** In previously collected cohort data ('Adolescent Pain in Aalborg-2011') adolescents (aged 12-19) completed an online questionnaire, including demographic data, current pain sites, sports participation, and HRQoL (assessed by Euro-QoL 5D-3L). Latent class analysis was used to classify spatial pain patterns, based on the pain sites. The analysis included 2,953 adolescents.

**Results:** Four classes were identified: (1) little/no pain (63% of adolescents), (2) majority lower extremity pain (10%) , (3) multi-site bodily pain (22%) , and (4) multi-site head and stomach (3%). The lower extremity multi-site pain group reported highest weekly sports participation ( $p<0.001$ ; mean: 2.9 days/week; 95%CI 2.7 to 3.2), while the multi-site bodily pain group and the multi-site head and stomach pain groups had lowest EQ-5D scores ( $p<0.001$ ). Males were more likely to belong to the little/no pain class, whereas females were more likely to belong to the multi-site bodily pain class.

**Conclusions:** Latent class analysis identified distinct classes of pain patterns in adolescents, characterized by sex, differences in HRQoL and sports participation. The class with multi-site bodily pain and reduced quality of life was the largest among adolescents reporting pain, , and future research on treatment strategies should consider targeting this group.

## INTRODUCTION

Musculoskeletal pain in adolescents is highly prevalent. A systematic review reported that up to 25% of adolescents experience musculoskeletal pain several days a week (King et al., 2011), although these estimates are limited by a large variability in how prevalence was assessed. Musculoskeletal pain is a common reason for youth to seek medical attention from their general practitioner, with up to 64% of adolescents' complaints continuing years later (El-Metwally et al., 2004), which will have a negative effect on physical activity, health related quality of life, anxiety, school attendance, participation in hobbies and social activities, and can cause disturbances in appetite, sleep and mental health (Rathleff et al., 2016, Brattberg, 2004, Fuss et al., 2011).

In adults, a greater number of pain sites appears to have a larger influence on physical fitness and social activities, in comparison to localized pain (Kamaleri et al., 2008), indicating the impact of pain may depend on how widespread pain it is. Indeed, having musculoskeletal complaints in more than one location is associated with poorer prognosis in adult patients in general practice (Bot et al., 2005, Kastelein et al., 2015, Smidt et al., 2006). Multi-site pain is common not only in adults (Kamaleri et al., 2009), with a high proportion of adolescents reporting pain in more than one site (Rathleff et al., 2013, Paananen et al., 2010, Mikkelsen et al., 2008).

An interesting consideration is potential systematic spatial patterns of co-occurring pain sites. Previous investigations have identified classes based on pain locations in adults, such as regional upper limb pain (with or without headache), regional lower limb pain, widespread whole body pain (Schmidt and Baumeister, 2007), and that certain patterns could be associated with other health factors (Lacey et al., 2015). It has been indicated that co-complaints commonly occur at adjacent areas (Hartvigsen et al., 2013), perhaps reflecting widespread spreading of pain due to facilitated pain mechanisms (Arendt-Nielsen and Graven-Nielsen, 2011, Graven-Nielsen and Arendt-Nielsen, 2010).

Less is known about co-occurring pain-sites in adolescents and children, with no research examining whether such patterns of multi-site pain sites exist in younger populations.

Identifying patterns of pain locations in adolescents could be an important consideration treating adolescent with multi-site pain. This aim of this study is to undertake an exploratory analysis evaluating if specific 'classes' of pain are evident in adolescents

reporting pain. A secondary aim will be to determine whether pain classes are associated with self-reported sports participation, body mass index (BMI), and quality of life, and whether there are sex differences between the classes. Sex was chosen, due to its previous relationship with different classes in adults.

## **METHODS**

### *Study design and population*

This was a cross-sectional analysis based on the Adolescent Pain in Aalborg (APA2011) cohort (Rathleff et al., 2013). This cohort was established in 2011 when adolescents aged 12-19 years from eight primary schools and four upper secondary schools in Aalborg were invited to participate in a questionnaire regarding pain, physical activity, and quality of life. The prevalence of pain at individual sites has previously been published (Rathleff et al., 2013), however no analysis regarding the patterns of multi-site pain were undertaken, as was the aim of the present study. Physical education teachers in the participating schools provided students with a link to the online questionnaires, and allocated 10 min during physical education for students to fill out the questionnaire. The study was approved by the North Denmark Region local ethics committee (N-20110020). The Ethics Committee did not require signed consent from each participant, but required that the schools informed the parents about the study and that participation in the study was voluntary. The reporting of this manuscript complies with the STROBE Statement for cross-sectional studies.

### *Questionnaire*

Full details regarding the online questionnaire administered have been published elsewhere (Rathleff et al., 2013). Briefly, the online questionnaire contained demographic questions on age, sex, height, weight and the school the participants attended. Participants were able to optionally enter a contact number (either theirs or their parents), although this was not compulsory. The adolescents were then presented with a pain mannequin, and were instructed to mark the regions where they currently experienced pain. Pain mannequins have previously been used in children, and appear to be appropriate to be completed unassisted in children older than 8 years of age (von Baeyer et al., 2011). The mannequin presented 12 potential regions where they could indicate current pain (Knee, Back,

Shoulder, Foot, Head, Shin, Hip/groin, Forearm/hand, Stomach, Thigh, Elbow, Chest). Afterwards, they were asked about the pain frequency in the regions they had selected. The pain frequency was divided into the following five categories: rarely; monthly; weekly; more than once per week; almost daily. After the pain mannequin questions, the adolescents were asked if they participated in sports outside of mandatory physical education classes. If they participated in sports, they were asked which types and how many times they participated per week. The last page of the questionnaire contained the Euro-QoL 5D (EQ-5D) which measures health related quality of life (HRQoL). The questionnaire for the adolescents aged 15–19 years contained the adult version of EQ-5D 3L. The questionnaire for the adolescents aged 12–14 years contained the youth version of the EQ-5D-Y.

### *Class analysis*

Latent class analysis (LCA)(Lanza et al., 2007, Yang, 2006) was used to determine classes of common co-occurring pain sites. LCA is a statistical tool used to identify homogeneous, mutually exclusive groups (or “classes”) that exist within a heterogeneous population. Latent class analysis is a class analysis appropriate for solely categorical variables (Lanza et al., 2007), and as such has previous been used in adults with pain (Hartvigsen et al., 2013, Schmidt and Baumeister, 2007) and chronic low back pain (Beales et al., 2012, Coenen et al., 2016).

LCA was conducted using the R Studio PoLCA package. As in previous studies in adults (Schmidt and Baumeister, 2007, Lacey et al., 2015), the anatomical location of pain sites was used for the analyses. First, to evaluate the potential classes within the data, a series of models were run and evaluated. LCA models were successively evaluated, based on the previous research in adult populations. Random seeds were used as starting values for each of the models. Each model was run from multiple different starting values to ensure that the maximum likelihood solution was correctly identified (Lanza et al., 2007). The optimal number of classes or ‘classes’ would be determined by comparing the Bayes Information Criterion (BIC) statistic and the Akaike’s Information Criterion (AIC) across the models. Plots pain probabilities by class were compared across starting for the selected model to ensure robustness. Class distinction was measured using class average posterior probabilities (AvePPs), where a value of above 0.7 represents clear separation (Lacey et al., 2015).

For each class in the chosen LCA model, the conditional probability of pain sites gives the probability that a participant in that class reported pain at specific site(s). These were used to allocate informative names for each class. Once optimal model and number of classes were identified, participants were assigned to the class for which they have maximum posterior probability of belonging to (Lanza et al., 2007). Class membership variables were retained for subsequent analyses.

### *Statistics*

Based on the classes identified, Chi squared tests were used to examine the association of classes with sex, and analysis of variance (ANOVA) was used to assess the differences between classes on participation in sports, BMI, and Euro- QoL 5D 3L. If significant, the ANOVA was followed by Bonferroni correction for multiple comparisons, and the 'No pain' group was used as the reference group, to reduce the risk type I error with multiple comparisons between groups. These tests were carried out using IBM SPSS Statistics (version 20). Data are presented as means and 95% confidence intervals in text and tables.

## **RESULTS**

### *Respondents*

4,007 adolescents aged 12–19 years were approached and 2,953 (73.7%) answered the questionnaire fully and were included in the data analysis. Ninety-nine did not participate, while 255 only partially completed the questionnaire and were excluded from the analysis. Of the responders, 1827 (61%) were female, (median age 17 years, IQR 16–18; mean height 167.2 cm, SD 6.9, and weight of 58.8 kg, SD 11.2).

In primary and lower secondary schools, the proportion of females varied from 43% to 67%, while in upper secondary schools, the percentage of females varied between 56% and 68% across the different schools, which reflects the true distribution of 61% females. As non-responders were equally divided across all age groups, there was no tendency for older or younger participants to not respond (Rathleff et al., 2013).

### *Characteristics of the classes*

There was no consensus between the BIC and AIC, with BIC indicating a two class model, and AIC indicating a five class model. Therefore, models with N=2-5 classes were considered for selection. A five class model was identified as the optimal model, with AIC being lowest for this solution (Table 1). In this model, one class was identified as residuals, with only 21 participants, and was excluded from further analysis, leaving four classes which will now be described. For this model, AvePPs ranged from 0.68 to 0.79, indicating distinction between classes. These classes were labelled as follows: (1) multi-site lower extremity pain; (2) little or no pain; (3) majority head and stomach pain; and, (4) multi-site bodily pain.

Figure 1 shows the class-specific probability for pain at each site, given membership for each of the four classes. Class 1 (9.7% of subjects, n = 292) is represented by multi-site pain (97.6%) with a median of 2 (IQR 1-3), and a high probability of having knee pain, followed by foot, shin, pelvis and thigh pain and was labelled 'majority lower extremity pain'. Class 2 (63.3%, n = 1902) had low probabilities of pain at all sites (<0.2), was characterised by participants with one or no pain-sites (median 0 pain sites; IQR 0-1), and was labelled 'little or no pain'. Class 3 (3%, N=90) was characterised by a high probability of head and stomach pain, had a high number of pain-sites (median 3; IQR 2-4), with 87% having multi-site pain, and was labelled 'multi-site majority head and stomach pain'. Class 4 (21.6%, n = 648) had a high probability of back pain, followed by knee, shoulder and head pain, was characterised primarily by multi-site pain (92%) with a median of 2 pain sites (IQR 1-3), and was labelled 'multi-site bodily pain' class.

### *Relationship between classes and sex, sports participation, HRQoL, and BMI*

Sex was associated with class membership ( $X^2(3,2932) = 74.3$ ,  $p < 0.001$ ); females were more likely than males to be in the multi-site bodily pain class (25.9% of females *versus* 15.9% of males), whereas males were more likely to be in the little or no pain class (73.1% of males *versus* 56.9% of females).

There were differences between classes for sports participation, HRQoL, and BMI (ANOVA:  $p < 0.001$ ; Table 2). Relative to the little or no pain class, all other classes had lower HRQoL. The multi-site bodily pain classes had higher BMI (mean difference = 0.6; 95% CI 0.3-0.9;  $p < 0.001$ ) and the multi-site majority lower extremity class had significantly higher weekly sports participation (Table 2).



## DISCUSSION

### *Classes of Pain in Adolescents*

The present findings demonstrate that adolescents with pain can be categorized into distinct classes, based on spatial patterns of their pain sites.

The group 'little or no pain' was characterised by low probabilities of pain at all sites. This means that individuals classified into this group reported no pain, or single site pain. The other classes were primarily characterised by pain multi-site pain, or pain in more than one location (all with >87% of their members having multi-site pain). The multi-site lower extremity pain class had higher probabilities of pain in the foot, shin, pelvis, and thigh compared to the 'multi-site bodily pain' group. The 'multi-site bodily pain' group had higher probability of back, shoulder and head pain. As the 'majority lower extremity' pain group reported the highest weekly sports participation, this may indicate regional lower extremity pain due to increased load from sports. This is supported by the fact that the pathogenesis of certain lower extremity injuries (such as knee pain), appear to be associated with increased joint loading (Rathleff et al., 2015). Overuse injuries are a common cause of chronic pain in adolescents with higher weekly sports participation being associated with an increased risk of sustaining overuse injuries (Junge et al., 2015, Kamada et al., 2016). The multi-site bodily pain class also had higher BMI and lower HRQoL, their pain may be more related to physical "underload" or deconditioning, (and perhaps in some cases overweight). Notably though, while this class had the highest BMI, it was still within the 'normal' range.

A small class of adolescents (N=90) characterised by the highest probabilities of head and stomach pain was also identified. While this class was primarily female (87%), it could be postulated that it results from menstrual pain or similar. Despite this, it is noteworthy that they reported the lowest health-related quality of life on the EQ-5D. However, no firm conclusions should be drawn, particularly because of the small size of this class.

The little or no pain class, and the multi-site bodily pain class had distinct sex differences. There was a significantly greater proportion of males allocated to the class with no / single pain site, whereas there was a greater proportion of females allocated to the 'multi-site bodily pain' class. This is perhaps expected, as females have a higher prevalence of musculoskeletal pain (King et al., 2011, Fayaz et al., 2016) and is similar to research in adult cohorts, where females are more likely to belong to pain classes with more widespread

pain (Schmidt and Baumeister, 2007). On the other hand, in the study by (Lacey et al., 2015), adult females were also likely to belong to classes with a higher count of pain sites.

#### *Differences from adult pain classes*

Studies have previously utilized latent class analysis in adult populations. Hartvigsen et al. (Hartvigsen et al., 2013) reported on pain classes for nine different primary pain sites in the general population. It was found that the most common class was pain at the primary site alone; followed by pain co-located at adjacent sites (Hartvigsen et al., 2013). This is similar in this adolescent cohort, whereby the largest class was the one with either no pain or pain at one site only. In an adult population Schmidt and Baumeister (Schmidt and Baumeister, 2007) used latent class analysis similar to the current study, based on pain from thirteen sites, identifying seven classes. The largest class (47% of their population) identified by Schmidt and Baumeister (Schmidt and Baumeister, 2007), was a group with a no/one painful site, reflecting the present results, and is similar to a study Lacey and colleagues (Lacey et al., 2015) in adults older than 50 years. Similar to the current investigation, Schmidt and Baumeister (Schmidt and Baumeister, 2007) also identified a regional lower extremity class, however, they also reported two additional upper body musculoskeletal pain groups, characterized by the presence or absence of headache, in addition to a prevailing headache group, and a widespread pain class (Schmidt and Baumeister, 2007). The greater number of classes identified, may have been because of differences in the sample size, as Schmidt and Baumeister (Schmidt and Baumeister, 2007) used data from >13000 participants.

Alternatively, it may also be representative of differences in the older age of the population; as number of pain sites increases with increasing age, this would increase the number of potential classes or patterns of pain to be reported.

#### *Typology of multi-site pain in youth and impact of identified classes*

Previous research has examined multi-site pain in youth, and it appears that those with more widespread pain are more likely to experience continued persistent pain (El-Metwally et al., 2004, Mikkelsen et al., 2008, Paananen et al., 2010). Indeed, regardless of pain frequency, multi-site pain has a greater impact on HRQoL. This is substantiated by data from adolescents with low back pain (LBP), showing that while pain itself is a prevalent symptom, overall it has low associated disability and little effect on HRQoL, but there is a subset of

adolescents in whom LBP is associated with whole body pain report significant impairment and deserve more attention (Pellise et al., 2009, Balague et al., 2012). This resonates well with our results, demonstrating a multi-site bodily pain group with the lowest HRQoL, in which a large proportion have back pain, together with pain in other locations.

Previous attempts to identify sub-groups of adolescent chronic pain patients using latent class analysis (Wager et al., 2014). The latent class analysis was based on pain intensity, school absences and pain-related disability less passive pain coping and affective pain perception. In contrast, the current study used a population-based sample of adolescents, representing a less severe population, as pain in schoolchildren has a more limited impact on function compared to clinical samples (Huguet and Miro, 2008). Identifying patterns of pain in those with multi-site pain, may present a simple meaningful way to sub-group the heterogeneous presentations of adolescents with pain in the general population. The current investigation builds on this previous research as this is the first study to identify classes of pain distributions in adolescents, and the classes displayed differences in BMI, sports participation and HRQoL, and are not identifiable purely by the number of pain sites. Further research is needed to evaluate whether the classes identified in this study are differentially associated with disability, prognosis, or pain later in life. For example, having back or head pain in adolescence is associated with an increased risk of pain in adulthood (Brattberg, 2004, Walker et al., 2010). It is not improbable that those with multi-site pain during adolescence may be more susceptible to chronic pain later in life. It is also possible to hypothesize that the identified classes, could represent a continuum of pain, whereby an individual's pain may begin in a single site (membership in either the no/single site class), and progress into one of the multi-site classes. This is plausible, given reports of nonspecific pain symptoms in childhood have been associated with a two-fold increase in risk of widespread pain onset over a 12-month period (Jones et al., 2003). However, the different classes could also represent differing aetiologies of pain. Further prospective data is needed to explore these hypotheses. Clinicians should consider when youth present with pain in a certain site (e.g. knee), if they have concomitant pain sites. For example, a youth with knee pain, may normally be treated with knee specific exercises for their knee pain, however, this may not be the most appropriate treatment approach for those with concurrent other lower extremity pain. Further research on the treatment of multi-site pain is required, before such recommendations can be made.

### *Limitations*

Although the AvePPs of the identified classes were high, indicating low chance of misclassification, not all participants will have 100% probability of belonging to their assigned class, and this uncertainty cannot be accounted for in the subsequent analyses. Although this method has previously been used in latent class analysis of pain sites in adults, this needs to be taken into account in interpreting the results stratified by classes. Additionally, the analysis divides the groups empirically; researchers label the groups based on their observations of the characteristics of the data for each of the classes. Some of the probabilities informing the clustering were low (e.g. < 30% of those in the multi-site bodily pain group had head pain). The cross-sectional nature of the study precludes casual conclusions to be drawn regarding the differences between the identified classes (although, it is very unlikely that the presence of pain would increase sports participation). Additionally, we did not have any information on whether pain was unilateral *versus* bilateral, traumatic *versus* non-traumatic, or on pain intensity preventing conclusions to be drawn on these parameters. This remains an exploratory analysis, which needs to be validated in a new external cohort in order to determine if similar classes can be replicated.

### *Conclusion*

This is the first investigation to determine whether classes are evident in a young adolescent population. Using latent class analysis, the data suggests four distinct classes of pain patterns in adolescents, characterized by differences in sex, BMI, sports participation, and health related quality of life. The class with multi-site bodily pain in adolescents and reduced quality of life represents a large portion (more than one fifth) of adolescents, and could direct future research for the management of this group. Further research is needed to replicate and validate these findings.

### **Author Contributions**

All authors contributed to the study design. MSR was responsible for collecting the data. SH conducted the latent analysis and drafted the manuscript. All authors critically revised the manuscript and approved the final version.

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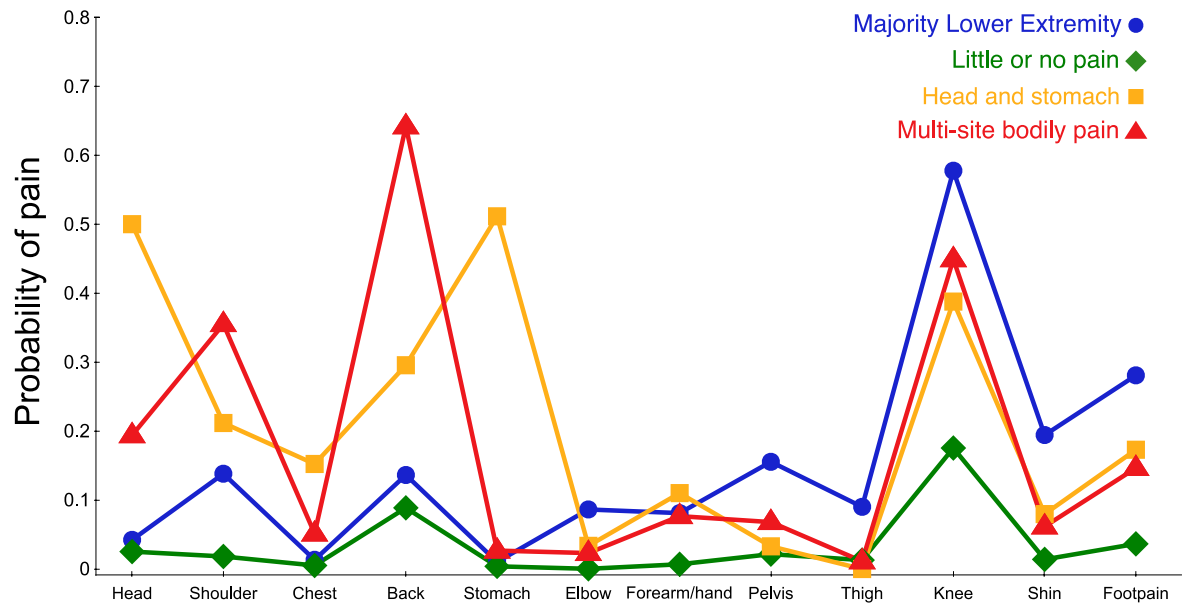
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1 **Figure Legends**

2

3 **Figure 1.** Probability of pain (0-1) in different body sites according to class membership



4



N CLASSES	BIC	AIC
2	19603	19454
3	19613	19385
4	19614	19308
5	19680	19296
6	19759	19297
7	19828	19288

**Table 1.** Model fit statistics for models consisting of 2 to 7 classes. BIC = Bayes Information Criterion; AIC = Akaike's Information Criterion. A smaller BIC and CAIC for a particular model suggests that the trade-off between fit and parsimony is preferable.

	Little or no pain	Majority Lower Extremity	Multi-site head and stomach	Multi-site bodily pain
<b>BMI (kg/m<sup>2</sup>)</b>	20.8 (20.7 – 21.0)	21.2 (20.8-21.6)	21.4 (20.6 - 22.2)	21.5 (21.3 - 21.8)*
<b>Sports Participation</b> (days/week)	2.2 (2.1 -2.3)	2.9* (2.7 -3.2)	2.1 (1.7 -2.5)*	2.3 (2.1 -2-4)
<b>EQ 5D index score</b>	0.92 (0.91-0.92)	0.79 (0.77 - 0.81)*	0.76 (0.73 -0.80)*	0.78 (0.77 - 0.79)*

**Table 2.** Description of clusters according to body mass index (BMI), weekly sports participation (number of days per week), and health related quality of life (measured by EQ 5D index score, 0-1 worst to best). Data are presented as mean (95% confidence interval).

\* Statistically different ( $p < 0.01$ ) compared with the little or no pain cluster.